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Enhanced Automatic Action Imitation and Intact Imitation-Inhibition in Schizophrenia

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Abstract

Imitation plays a key role in social learning and in facilitating social interactions and likely constitutes a basic building block of social cognition that supports higher-level social abilities. Recent findings suggest that patients with schizophrenia have imitation impairments that could contribute to the social impairments associated with the disorder. However, extant studies have specifically assessed voluntary imitation or automatic imitation of emotional stimuli without controlling for potential confounders. The imitation impairments seen might therefore be secondary to other cognitive, motoric or emotional deficits associated with the disorder. To overcome this issue, we used an automatic imitation paradigm with non-emotional stimuli to assess automatic imitation and the top-down modulation of imitation where participants were required to lift one of two fingers according to a number shown on the screen whilst observing the same or the other finger movement. In addition, we used a control task with a visual cue in place of a moving finger, to isolate the effect of observing finger movement from other visual cueing effects. Data from 33 patients (31 medicated) and 40 matched healthy controls were analyzed. Patients displayed enhanced imitation and intact top-down modulation of imitation. The enhanced imitation seen in patients may have been medication induced as larger effects were seen in patients receiving higher antipsychotic doses. In sum, we did not find an imitation impairment in schizophrenia. The results suggest that previous findings of impaired imitation in schizophrenia might have been due to other cognitive, motoric and/or emotional deficits.

Keywords: social influence, social cognition, mimicry, top-down control, antipsychotic medication

Introduction

Imitation refers to the translation of perceived actions into executed actions[1]. Imitation is a likely foundation for important social behaviors, ranging from social learning (e.g. skill or language acquisition) to the ability to understand the intentions and feelings of others[2]. Imitation also contributes to smoothness, predictability, and feelings of affiliation in social interactions[3, 4]. As such, research on imitation is crucial for understanding disorders that are characterized by impairments in social behavior, and may provide a better understanding of the underlying deficits involved in such conditions.

Patients with schizophrenia (SCZ) display impairments that may involve imitation-related systems, including understanding the intentions and feelings of others[5] and they tend to have difficulties with social interactions[6]. Behavioral studies on imitation in schizophrenia suggest that patients are impaired at imitating others[7-12] and it has been suggested that schizophrenia constitutes a disorder of imitation[13]. However, there is clear heterogeneity between studies when looking at the biological foundations of the impairment. Some imaging and transcranial magnetic stimulation (TMS) studies find intact activity[14-17] in the mirror neuron system (MNS)[1] – which is thought to form the neural basis of imitation[18-21] - during action observation and execution; while others find this activity to be reduced[22, 23], altered[13] or enhanced[14, 24] .

Several issues also remain unresolved with respect to the behavioral studies. Experimental work within this area can be roughly categorized into four domains: imitation can either be voluntary or automatic, and it can be of either emotional (e.g. facial expressions) or non-emotional stimuli (e.g. manual movements). Studies have primarily focused on *voluntary* imitation where participants e.g. are required to imitate certain movements. This research has consistently shown that patients make more errors when asked to imitate facial and manual movements[8-10, 25-28] and facial expressions[7, 10, 26, 29-31] compared to healthy individuals.

[1] Core MNS circuitry: the *pars opercularis* of the inferior frontal gyrus and adjacent ventral premotor cortex (Brodmann area 44 and 6) and the rostral inferior parietal lobule as well as the superior temporal sulcus, which processes biological motion.

Meanwhile, research on automatic imitation has been limited, in particular when it comes to imitation of non-emotional stimuli. Such research is important for three main reasons. First, voluntary tasks are (to varying degrees) taxing on a range of cognitive processes which are known to be impaired in schizophrenia[32], but which are not specifically tied to imitation. For instance, voluntary imitation requires working memory, attention to detail, planning, and self-monitoring of accuracy. It is therefore unclear whether the imitation impairments seen are due to specific imitation deficits, or due to general cognitive deficits which, among other things, should also be expected to impact voluntary imitation. Automatic processes, on the other hand, are generally much less taxing on such cognitive processes.[33]

Second, assessing someone's ability to voluntarily imitate is not the same as assessing their *tendency* to imitate or potential difficulties in the ability to inhibit *involuntary* imitation. This is important, because reduced imitation tendency may result in worse social interactions[3] while over-imitation may result in catatonic symptoms like echolalia or echopraxia seen in schizophrenia[34, 35]. The top down modulation of imitation and the MNS is subserved by structures related to perspective taking or mentalizing (including medial prefrontal cortex (mPFC) and temporo-parietal junction (TPJ)) as well as structures related to general cognitive control processes. Imitation-inhibition and general inhibition processes are thus thought to be at least partially distinct[36-44] . Interestingly, reduced top-down modulation of imitation has also been associated with reduced mentalizing and perspective-taking ability[36, 40], abilities known to be impaired in schizophrenia[45].

Third, because patients display a variety of problems in processing of emotions[46], it is unclear whether a deficit in voluntary or automatic imitation of emotional stimuli[11, 12, 47, 48] would reflect a specific impairment in imitation, or other aspects of emotion processing: e.g. differences in visual processing of faces (avoiding salient regions like the eyes and the mouth)[49], the experience of emotional states, or emotional reactions to the stimuli[50]. For instance, a characteristic symptom in schizophrenia is blunted affect[29, 51]. This makes it difficult to distinguish between direct effects of action observation on action execution (imitation) and those mediated by emotional states.

Automatic imitation of non-emotional stimuli has not been studied experimentally in patients with schizophrenia and would overcome the limitations mentioned above. We therefore set out to investigate whether the basic mechanisms of imitation, and the top-down modulation of these (imitation-inhibition) is altered in schizophrenia, compared to healthy individuals.

Participants were asked to perform an automatic imitation task[52], where they performed certain finger movements according to the number shown on a screen, whilst observing the same or another finger move on the screen. Although the performed finger movements are voluntary, any effect of imitation on these is accidental since participants are not instructed to imitate, and general imitation results in poorer task performance. By assessing automatic processes we effectively reduce the cognitive load; however, lower level attentional processes are still recruited and may be affected in schizophrenia. We therefore included a control task[52] to be able to delineate imitation and imitation-inhibition from any attentional deficits or deficits in distractor-inhibition (for detailed task description see Methods). This also allowed us to control for any motor deficits.

We predicted that patients would have slower reaction times (RTs) and make more errors than healthy individuals, since patients display cognitive[32] and motor deficits[53] (e.g., psychomotor slowing/reduced processing speed[54]). Importantly, we had four core research questions (i – iv), we wanted to answer: we were interested in determining whether patients would show deficits beyond those that could be attributed merely to other cognitive or motoric deficits, indicating a specific deficit in either i) basic imitation or ii) the top-down control of it (i.e. imitation-inhibition). In addition, since two recent studies[13, 22] indicate that antipsychotic medication might normalize putative mirror neuron activity (MNA) during action observation and imitation, we assessed whether iii) imitation or iv) imitation-inhibition tendency in patients was associated with antipsychotic medication dose. Finally, in case of group differences in imitation or imitation-inhibition, we were interested in assessing whether these were associated with the patients' level of functioning.

Methods

Participants

Thirty-nine patients with an ICD-10 DCR diagnosis of schizophrenia or schizoaffective disorder and forty matched healthy controls were included in the study. Diagnosis was confirmed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[55, 56]. Controls were pairwise matched to the patients according to age, gender, childhood residence as well as commenced educational level and parental socioeconomic status when possible (see Table 1). Two of the controls were matched to patients that had to be excluded as they did not fulfil inclusion criteria and one patient did not have a matched control as they did not complete the whole study.

Patients were recruited through the Psychiatric Centre of the National Hospital of the Faroe Islands. Controls were contacted based on their age and gender and, if they fulfilled the inclusion criteria and matched a patient, were offered to participate in the study. Participants were between 18 and 55 years old. Exclusion criteria included: current psychoactive substance use disorders (except nicotine), a neurological or medical disorder that could affect brain functioning, and an estimated IQ below 70 based on prior history or testing. In addition, the controls were excluded if they or a first-degree relative had a history of severe mental disorder. The participants were screened for recent use of psychoactive substances (THC/cannabis, opiates, amphetamine, MDMA, benzodiazepines, cocaine) using a urine stick (NanoSticka® 200-32). Patients, without a prescription who had a positive test, were excluded. None of the controls had a positive test. At the time of testing, all but two patients were taking antipsychotic medication. We converted antipsychotic doses to chlorpromazine (CPZ) equivalents[57, 58] (see Table 1S for details). Some patients also took other types of medication (see Table 2S).

Six patients had hand tremor which made it difficult or impossible for them to keep their fingers stable enough to complete the task. Data from these was excluded from the analysis. Data from 33 patients and 40 controls were included in the analysis.

General Procedure

The imitation task was administered as part of a larger battery of cognitive tasks. In addition, symptom severity and level of functioning were assessed with the Scale for the Assessment of Positive/Negative Symptoms (SAPS/SANS)[51, 59] and the Personal and Social Performance Scale (PSP)[60], respectively (see Table 1). The study complied with the ethical standards of the relevant national and institutional committees and with the Helsinki Declaration. Written informed consent was obtained from all participants after the procedure had been explained.

Imitation and Effector Priming Control Task

The task is a modified version of the automatic imitation and effector priming control tasks described in Cook & Bird (2011)[52]. Briefly, short video sequences of a human hand were presented on a computer screen (see Figure 1) comprising 4 different conditions in a 2 x 2 factorial design with the factors task (imitation or control) and congruency between the targeted finger on the screen and the required finger movement (congruent or incongruent finger). There were 120 trials in total, 30 for each condition.

Participants were required to place the index and middle fingers of their right hand on the number 1 and 2 (letter N and M on the keyboard), respectively. On each trial, participants had to lift either their index or middle finger as fast as possible according to the number shown on the screen and then replace it on the same key: if "1" was shown, they had to lift their index finger and if "2" was shown, they had to lift their middle finger.

In the imitation task (see Figure 1a) half of the trials depicted an action that was congruent with the required finger movement (e.g. index finger lift required and index finger lift shown) and the other half were incongruent. Similarly, in the control task (see Figure 1b), on half of the trials a semi-transparent green mask appeared on the finger corresponding to the instructed finger movement (congruent trials), and on the other half the mask appeared on the opposite finger (incongruent trials, e.g. index finger lift

required and mask appeared on the middle finger). During the control task the fingers remained still for the whole trial. Trials were pseudo-randomized so that the same trial type never occurred more than twice in a row. In order to differentiate automatic imitation from spatial compatibility[52], response movements were orthogonal to stimulus postures (see Figure 1). The task was programmed in Presentation v. 16.3 (Neurobehavioral Systems).

Before the testing, participants were given standardized instructions and a practice session where they had to make 8 correct responses in a row to ensure their ability to perform the task. The whole process took approximately 15 min.

Data Analysis

As in Cook & Bird (2011)[52], RTs shorter than 150 ms and longer than 2.000 ms were excluded from the analysis. In addition, error-trials in which the participant lifted the incorrect finger were removed from the RT analyses. All analyses were run using mixed effects regression models. To assess whether there was a specific imitation (question i) or imitation-inhibition (question ii) deficit in schizophrenia beyond non-specific cognitive or motoric deficits, we ran two separate models with RTs as outcome and group (schizophrenia, control) by task (imitation, control) as predictors, including only congruent trials to answer question i and only incongruent trials to answer question ii (see Table 2). The analyses accounted for the pairwise matching of participants (when present), by assigning the matched individuals a common identifier and entering it as a random intercept. Random slopes were included for group, task and finger (index vs. middle finger).

To assess whether there was an association between antipsychotic medication dose and imitation (question iii) or imitation-inhibition (question iv), we ran two separate models in the patients only with RTs as outcome and medication dose by task (imitation, control) as predictors, including only congruent trials to

answer question iii and only incongruent trials to answer question iv (see Table 3). Random slopes were included for task and finger.

Finally, follow up control analyses were run to assess whether a potential group difference could be due to generally slower RTs in patients (Table 6S patients, 7S controls) and whether any medication effects would still hold when excluding patients with recent antipsychotic medication changes and when controlling for potential confounders such as other medications (Table 8S), symptom severity (Table 9S) or level of functioning (Table 10S). Here we also assessed whether a group difference in imitation or imitation-inhibition was associated with level of functioning in the patients (Table 10S). A full description of these models as well as the models assessing that the task worked as expected can be found in the Supplementary Material Tables 4S – 10S. Note, that effect sizes are reported in the form of standardized beta coefficients for all linear models. In case of null results on theoretically meaningful comparisons, we performed a follow-up Bayes Factor (BF) analysis on the mixed effects models to assess the evidence in favor of the null hypothesis, with values below 0.3 indicating substantial evidence in favor of the null. For a more detailed explanation of mixed effects models, BF and the computational implementation, cf. Supplementary Material.

Results

Errors and Reaction Times

As predicted, patients made more errors than controls (SCZ: 8.79%, M = 10.55, SD = 7.47; controls: 5.27%, M = 6.33, SD = 6.44). This was the case for all three types of errors: wrong finger lifted (β = 0.61, SE = 0.16, z = 3.74, $p < 0.001$), RTs shorter than 150 ms (β = 0.98, SE = 0.23, z = 4.34, $p < 0.001$), and RTs longer than 2000 ms (β = 0.29, SE = 0.13, z = 2.27, $p = 0.023$). Patients also displayed slower RTs across conditions compared to controls (SCZ: M = 592 ms per trial, SD = 114.97; controls: M = 534.91 ms, SD = 62.66; β = 0.37,

SE = 0.14, t = 2.73, p = 0.01). For details on the error rate for each type of error by condition and group, see Table 3S.

Imitation Effect: Movement Facilitation due to Imitation vs a Control Cue

When assessing imitation in the two groups (question i), we compared RTs (outcome) in the two tasks (imitation, control) by group (predictors), looking at congruent trials only. Controls responded significantly faster to imitation trials compared to control trials. In addition, there was a significant interaction between task and group on RT (see Table 2: congruent trials). Specifically, patients showed an even larger difference in RTs between imitation and control trials than the healthy controls, see Figure 2a.

To assess whether this larger difference seen in the patients could be due to their generally slower RTs, we assessed the interaction between mean RT during congruent control trials and task (imitation vs control) in the two groups separately. For the patients, there was a significant interaction, where the slower the RT, the larger the difference between imitation trials and control trials (β = -0.25, SE = 0.08, t = -3.22, p = 0.002, Table 6S). In contrast, there was no such relationship in the controls (β = 0.07, SE = 0.10, t = 0.65, p = 0.518, BF = 0.07, Table 7S).

Imitation-Inhibition Effect: Inhibition of Imitation vs a Control Distractor Cue

Next, we looked at whether the groups responded differently to imitation-inhibition vs distractor-inhibition (question ii), by comparing incongruent trials in the two tasks. Controls had similar RTs during inhibition of imitation and distractor cue (BF < 0.001) and there was no significant interaction between task and group (BF = 0.07, Table 2: incongruent trials), see Figure 2b.

Imitation Tendency, Antipsychotic Medication Dose and Level of Functioning

Finally, we assessed the influence of antipsychotic medication dose on imitation (question iii) and imitation-inhibition (question iv). We first looked at congruent trials in the two tasks (imitation, control) for the

patients (question iii). We observed a significant interaction between task and medication dose on RTs. Specifically, patients receiving a higher dose showed faster RTs during imitation vs control trials (see Table 3: congruent trials). This effect could not be easily explained by slower RTs in patients receiving higher doses, as there was no significant association between RT on congruent control trials and medication dose (β = 0.17, SE = 0.14, t = 1.2, p = 0.24, BF = 0.46). The interaction between task and medication dose remained significant when excluding the four patients, who had changes made in their antipsychotic medication within the last 3 weeks prior to testing and adjusting for other types of medication (Table S8), for symptom severity (Table S9) or for level of functioning (Table S10). Note, that there was an interaction between level of functioning and task in this last model, i.e. the higher the level of functioning, the faster RTs during imitation vs control trials (β = -0.14, SE = 0.06, t = -2.18, p = 0.032, Table S10 and Figure S1). When analyzing the incongruent trials (question iv), there was no significant interaction between medication dose and task (BF = 0.22, see Table 3: incongruent trials).

Discussion

This study investigated automatic imitation and top-down modulation of imitation in schizophrenia. We found that patients with schizophrenia, although generally slower, displayed enhanced automatic imitation and intact imitation-inhibition compared to matched healthy individuals. The fact that we did not observe reduced imitation in schizophrenia stands in marked contrast to previous reports of imitation impairments in this patient group. However, previous studies assessed either voluntary imitation[7-10, 25-31] or automatic imitation of emotional stimuli[12, 13, 32, 33] while not controlling for the cognitive, motoric and/or emotional deficits associated with the disorder. Thus, it is not possible to assess whether the imitation deficits seen in previous studies were primary or secondary to the aforementioned general deficits. By using an imitation task with non-emotional stimuli and a control task, we were able to delineate imitation-based effects from non-specific cognitive or motoric effects. Indeed, when controlling for these confounders, patients with schizophrenia do not display the reduced imitation suggested by previous studies. This finding is in line with

imaging and TMS studies showing intact[14-17] or even enhanced[14, 24] MNS activity in patients during action observation or imitation and with work done on social motor coordination in schizophrenia, where spontaneous coordination is preserved[61].

It could be argued that the enhanced imitation seen in patients actually reflects over-imitation. Indeed, over-imitation is sometimes seen in schizophrenia in the form of symptoms like echolalia or echopraxia[31, 32]. However, there are several factors that suggest that this was not the case. First, patients generally had slower RTs. This may have left more room for "improvement" compared to the controls, i.e. the controls could not respond much faster than they already were (floor-effect). The association between longer RTs and larger imitation effect in the patient group supports this hypothesis. Second, there was an association between higher antipsychotic dose and a larger imitation effect even when controlling for potential confounders such as symptom severity. This suggests that the enhanced imitation seen may be medication induced rather than a consequence of the disorder. Third, the larger the patient's tendency to imitate, the higher the level of functioning was seen. This is opposite to what would be expected if the increased imitation indeed reflected a deficit and rather suggests that increased susceptibility to social influence is an advantage for the patients. While no patients with symptoms like echolalia and echopraxia were present in our sample, we would expect them not to show enhanced imitation, but more likely impaired ability to inhibit imitation, consistent with studies on patients with frontal lesions[40] which may also display symptoms of over-imitation[62]. Future studies should test this hypothesis in patients displaying such catatonic symptoms.

The association between higher antipsychotic medication dose and increased imitation tendency is consistent with findings of increased MNS activity when receiving higher doses of antipsychotic medication[13] or when being on antipsychotic medication (compared to off)[22]. In these studies medication was associated with activity more similar to that of the healthy controls, suggesting a therapeutic effect. The underlying mechanism is not understood. We speculate that it could reflect the oxytocin-enhancing

effect of antipsychotics[63, 64]. Indeed, oxytocin has been shown to enhance MNS activity in healthy individuals[65, 66] and in patients with schizophrenia[67], and to increase imitation[68, 69]. Future studies could explore this relationship further.

There are certain limitations of our interpretation. First, 31 out of 33 patients were medicated. It is therefore unclear whether unmedicated patients would display similar behaviors as controls. Second, as patients were not randomized to different types or doses of antipsychotic medication, we cannot exclude that unmeasured individual differences accompanying medication dose contributed to the observed effects.

In conclusion, we did not find reduced imitation in schizophrenia. Rather, patients displayed enhanced imitation and intact imitation-inhibition. The enhanced imitation may have been medication induced. The results suggest that previous findings of impaired imitation in schizophrenia may have been secondary to other cognitive, motoric and/or emotional deficits and that schizophrenia should not be conceptualized as a disorder of imitation. These findings could have important implications for how the imitation system might be harnessed to facilitate social learning and interaction in patients with schizophrenia, as well as contribute to a growing mechanistic model of the social deficits accompanying the disorder.

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Tables & Figures

Table 1. Demographic and Clinical Characteristics of Patients and Controls

	Schizophrenia (n=33)	Controls (n=40)
Age, mean (SD)	36.7 (10.1)	39.3 (10.5)
No. of males : females	22 : 11	27 : 13
No. of right : left handed	30 : 3	36 : 4
Educational level commenced[a], mean (SD)	2.1 (0.6)	2.3 (0.7)
Years of education, mean (SD)	12.1 (2.6)	14.4 (3.2)
No. of high : middle parental SES[b]	11 : 22	13 : 27
Level of functioning (PSP), mean (SD)	57.5 (15.7)	86.1 (5.1)
Positive symptoms (SAPS)[c], mean (SD)	4.8 (4.2)	-
Negative symptoms (SANS)[d], mean (SD)	8.15 (4.9)	-
CPZ equivalent dose in mg, mean (SD)	809 (687)	-

[a]Educational level commenced divided into 4 levels: 1: primary school (up to 10 years of education), 2: secondary school/professional training, 3: bachelor program, 4: master program. [b]Parental socioeconomic status (SES) was divided into 3 levels, however none of the parents had a low SES. [c]SAPS is the total score of the 4 global items. It was not possible to obtain a SAPS score for one of the patients. [d]SANS is the total score of the 5 global items.

Table 2. Interaction between group and task on reaction time during i) congruent trials or ii) incongruent trials. The two models were defined as: $RT = \beta 0_i + \beta 1_i Task + \beta 2_i Group + \beta 3 TaskGroup + \varepsilon$.

Factor	ß	SE	t	P
Congruent trials				
Intercept	-0.22	0.05	-4.24	<0.001
Task	-0.09	0.03	-2.48	0.014
Group	0.39	0.13	2.99	0.005
Task × Group	-0.11	0.05	-2.32	0.021
Incongruent trials				
Intercept	-0.04	0.07	-0.64	0.521
Task	0.02	0.04	0.63	0.531
Group	0.48	0.15	3.27	0.001
Task × Group	-0.07	0.05	-1.29	0.195

Table 3. Interaction between task and antipsychotic medication dose (CPZ) on reaction time during iii) congruent trials or iv) incongruent trials. The two models were defined as: $RT = \beta 0_i + \beta 1_i Task + \beta 2 CPZ + \beta 3 TaskCPZ + \varepsilon$.

Factor	ß	SE	t	P
Congruent trials				
Intercept	0.21	0.13	1.65	0.110
Task	-0.20	0.05	-4.17	<0.001
CPZ	0.17	0.14	1.18	0.245
Task × CPZ	-0.13	0.05	-2.47	0.015
Incongruent trials				
Intercept	0.34	0.13	2.68	0.012
Task	-0.04	0.06	-0.76	0.454
CPZ	0.05	0.15	0.38	0.708
Task × CPZ	0.09	0.07	1.27	0.215

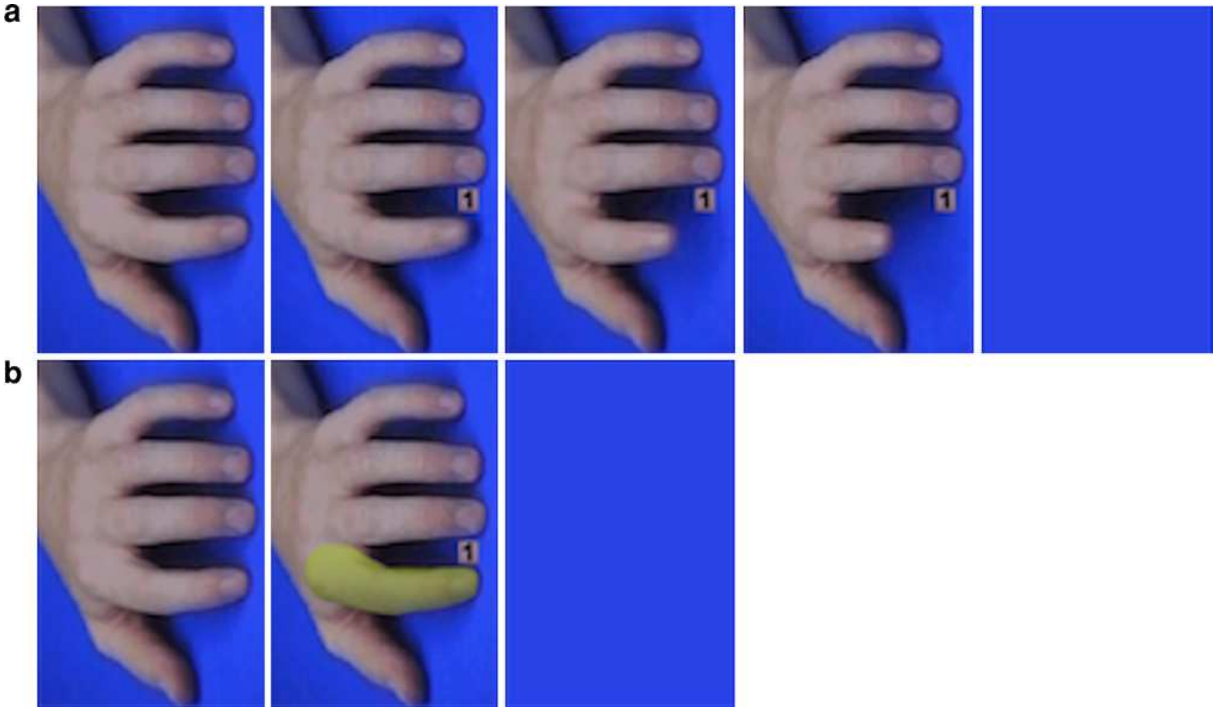

Figure 1. Example of the five frames shown in the imitation task (a) and the three frames shown in the control task (b). Both examples are from congruent trials. The first frame in both tasks displayed a resting hand that was shown for 800 - 2.400 ms. In the imitation task, the second (34 ms), third (34 ms) and fourth frame (500 ms) displayed the number 1 or 2 between the two fingers and the lifting movement of one of the fingers. In the control task, the second frame displayed the number 1 or 2 between the two fingers and one of the fingers was covered by a mask (display time: 568 ms). The last frame in both tasks was a blue screen, which remained on the screen until the participant had placed both fingers back on the keyboard. In both tasks, this blue screen appeared when the participant lifted the finger. Reprinted from Cook & Bird (2012)[70].

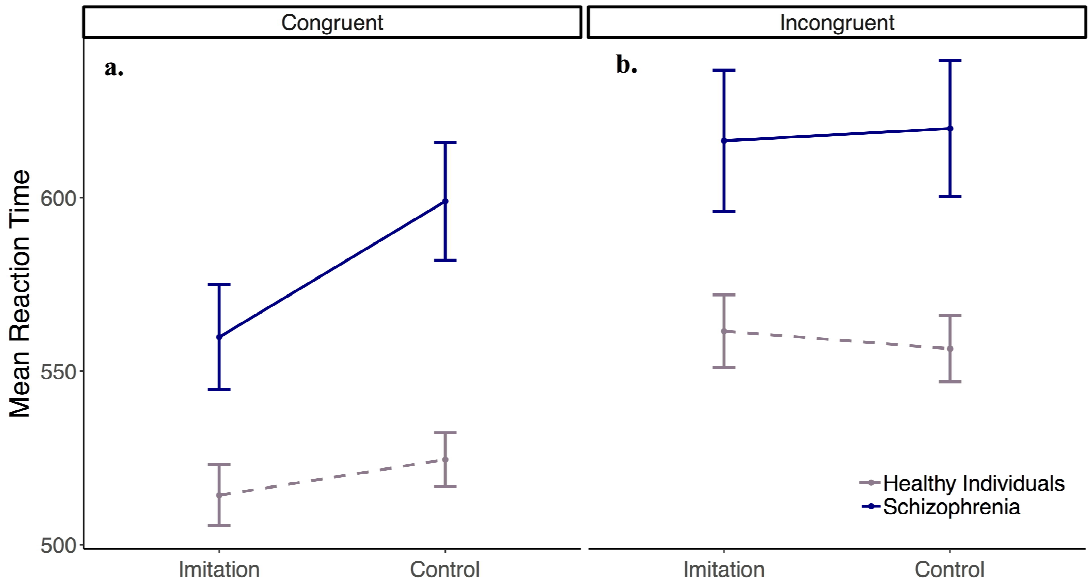

Figure 2. Mean reaction times (RTs) during congruent (a) and incongruent trials (b) in the imitation and control tasks for each group. Error bars: ±1 standard error of the mean (SE).

Supplementary Material

Table 1S. Chlorpromazine (CPZ) 100 mg/day dose equivalency

Antipsychotic medication	mg per day/injection	no. of patients[d]
Oral		
Amisulpride[c]	116.3	1
Aripiprazole[b]	4	10
Chlorprothixene[c]	83.3	2
Clozapine[c]	66.7	5
Olanzapine[b]	3	9
Quetiapine[b]	60	6
Risperidone[b]	0.8	2
Zuclopenthixol[c]	8.3	3
Depot[a]		
Paliperidone[b]	15	2
Perphenazine decanoate[c]	41.4	1
Risperidone[b]	10	3
Zuclopenthixol decanoate[c]	66.4	3

[a]Depot antipsychotics were first converted to oral equivalencies of the same drug using suggested equivalencies based on studies of oral to depot switch[1] or manufacturer's recommendation[2, 3] and then converted to CPZ equivalents (see note [b] and [c]). For perphenazine decanoate we used the average minimum effective dose of perphenazine decanoate[4] and equated it with the lowest recommended target dose of oral perphenazine[5] and then converted to CPZ equivalents (see note [c]). [b]For the second-generation antipsychotics, we used Leucht et al. (2014)[6] to convert to CPZ equivalents when possible except for clozapine where the conversion result was highly questionable. [c]For other antipsychotics (including clozapine), we used Gardner et al. (2010)[5] to convert to CPZ equivalents. [d]Seventeen patients were taking one antipsychotic, 12 were taking two, two were taking three. Twenty-seven patients had been on a stable dose for at least 3 weeks prior to the day of testing, while four patients had adjustments made (one patient discontinued use of the second and third antipsychotic, two had a down-regulation of dose, and one had an up-regulation of dose).

Table 2S

Medication type	no. of patients
Antidepressant	10
Anticholinergic	7
Corticosteroid	6
Anticonvulsant	4
Hormonal contraceptive	4
Proton pump inhibitor	4
Benzodiazepine (BDZ)	3
NSAID	3
Simvastatin	3
Antibiotic	2
Antidiabetic	2
Melatonin	2
Antabus (Disulfiram)	1
Antifungal	1
Anxiolytic non-BDZ	1
Betablocker	1
Levothyroxine	1
Opioid	1
Paracetamol	1

Models and Implementation

All analyses were performed with mixed effects regression models (also called multilevel or hierarchical regression models). We chose to use mixed effects models because of their flexibility in dealing with complex interdependencies in the data (e.g. participant matching, repeated measures by participant), as well as robustness in dealing with unbalanced and missing data. Mixed effects models combine fixed effects (analogous to traditional statistical predictors) and random effects, that is, effects that are allowed to vary e.g. by participant. In other words, participants are not assumed to display the same effects, e.g. by experimental condition, but might display different effects. Random effects are partially pooled, that is, a common underlying distribution is assumed, which partially constrains the possible variability of individual participants, and can further be used to compensate for unbalanced and missing data (for in depth discussion of these issues and a mathematical formalization, see:[7-9]. In order to determine the most appropriate regression family and link for the analyses of reaction time (RT), we performed a comparative distributional fit analysis of the RT by participant, comparing Gaussian, log-linear and gamma distributional fits to the data using Bayesian Information Criterion. Since no distribution was significantly better than the Gaussian distribution, we chose to employ linear mixed effects regressions (post-hoc we tested log-linear and gamma mixed effects regressions and obtained analogous results to those we reported in the paper). When

analyzing errors, we used Poisson regression with a log link (count variable). Analyses were performed in R 3.4.1[10] using lme4 1.1-13[11]. Residuals were assessed with DHARMa[12]. Influential data points were checked with leave-one-out diagnostics[13]. When the groups were compared, the binary variable group (control vs. schizophrenia) was included as a fixed effect in addition to the task relevant variable.

The statistical models explicitly accounted for the one-to-one matching of patients and controls, when present. Each pair and unmatched participant was given a common identifier and included as random intercept in the model. This allowed us to include unmatched participants and rely on the additional data to reduce uncertainty in the estimates[7]. Crucially, we allowed the tightness of the match to vary; that is, we did not assume all one-to-one matches to be exactly the same across pairs. We did so by including a random slope for group on the pair random intercept. This procedure explicitly estimates the within-pair level of non-independence introduced by matching and adjusts standard errors accordingly, which is a more conservative procedure than just assuming homogeneous matches. Analogously, we included random slopes for congruency and task, when present in the model, and for finger (index vs. middle finger).

To minimize convergence issues in the estimation of the models, we centered and scaled all linear continuous variables. If convergence issues still happened, we simplified the random structure removing one random slope at a time until model estimation converged. Full model specifications and parameter estimates for each analysis are reported in full in Tables 2 and 3 in the paper as well as 4S to 10S. Note, that effect sizes are reported in the form of standardized beta per each predictor for all linear models. Standardized beta coefficients indicate effect sizes in terms of standard deviations (so, for instance, in case of a binomial predictor such as group, they become equivalent to Cohen's d) when controlling for all other predictors included in the model. By reporting standardized effect sizes, we make it easier to comparatively assess the effects of different predictors (which are often on different scales).

Note, for the binomial variable Group, healthy controls were set as baseline; i.e., the effects of group are to be interpreted as the difference between patients with schizophrenia and controls, with positive beta values indicating higher outcome values for patients compared to controls and negative beta values indicating lower outcome values. This also means that beta values of the intercept and other predictors (e.g. Task) are to be interpreted as effects for the control group. Similarly, the control task was set as baseline for the Task variable and congruent trials as baseline for the Congruency variable.

In case of null results on theoretically relevant questions, we performed a follow-up Bayes Factor (BF) analysis to assess the evidence in favour of the null model. We followed the procedure in Rouder and Morey (2012) for linear models with mixed effects (BayesFactor 0.9.12-2.) which employs Liang uninformative priors[14, 15]. A BF below 0.33 was interpreted as substantial evidence in favour of the null hypothesis, a BF above 3 as substantial evidence in favour of the alternative hypothesis, with values below 1 and approaching 0.33 favouring the null over the alternative and vice versa. Values close to 1 did not favour one over the other[16, 17].

Table 3S – Mean (SD) number of errors for each condition within each group, distinct by error type: miss (the wrong finger was lifted), short (RTs < 150 ms), long (RTs > 2000 ms). Error analyses for each type of error separately revealed similar patterns as the reaction time analyses with no significant differences between groups when comparing different conditions (results not shown).

	Imitation Task Congruent	Imitation Task Incongruent	Control Task Congruent	Control Task Incongruent
Controls (Miss)	0.50 (0.68)	1.43 (1.57)	0.57 (0.96)	1.10 (1.39)
Schizophrenia (Miss)	1.39 (1.46)	2.32 (2.41)	1.00 (1.04)	2.11 (1.96)
Controls (Short)	0.62 (1.03)	0.55 (0.90)	0.60 (1.06)	0.82 (1.17)
Schizophrenia (Short)	1.89 (2.46)	1.63 (2.58)	2.00 (2.77)	1.53 (2.33)
Controls (Long)	0.50 (0.78)	1.02 (0.95)	0.48 (0.82)	1.20 (1.26)
Schizophrenia (Long)	0.66 (0.78)	1.47 (1.52)	0.97 (1.05)	1.45 (1.22)

Imitation and Effector Priming Control Task

To assess whether the tasks worked as expected, i.e. incongruent trials resulted in longer RTs than congruent trials, we compared RTs in the two conditions (incongruent, congruent) for the imitation task and the control task separately across all participants. This was indeed the case: incongruent vs. congruent trials in healthy individuals in the imitation task $\beta = 0.33$, SE = 0.04, $t = 8.55$, $p < 0.001$, Table 4S) and the control task $\beta = 0.19$, SE = 0.04, $t = 4.74$, $p < 0.001$, Table 5S). This relationship was similar for both groups, i.e. the group by congruency interaction was not significant and there was substantial evidence in favor of the null-hypothesis of no group difference both within the imitation and the control task (ps ≥ 0.12, BFs < 0.15, see Table 4S and 5S).

Table 4S – Interaction between group and congruency on reaction time during imitation trials. The model was defined as: $RT = ß0_i + ß1_i Congruency + ß2_i Group + ß3 CongruencyGroup + \varepsilon$, where ßs are the regression coefficients and the subscript i indicates that they are allowed to partially vary by participant pair (or participant when analyzing data from one group only) – in other words, that they are included as both fixed effects and random slopes by participant pair - and ε is the error term. Note that in this model and in all the following ones correlations between random effects were explicitly modelled and estimated. We do not include the correspondent covariance matrix within the model equations reported to avoid unnecessarily complicating them.

Factor	ß	SE	t	p
Intercept	-0.30	0.06	-4.84	<0.001
Congruency	0.33	0.04	8.56	<0.001
Group	0.36	0.14	2.65	0.012
Congruency × Group	0.08	0.05	1.54	0.125

Table 5S – Interaction between group and congruency on reaction time during control trials. The model was defined as: $RT = ß0_i + ß1_i Congruency + ß2_i Group + ß3 CongruencyGroup + \varepsilon$.

Factor	ß	SE	t	p
Intercept	-0.24	0.05	-4.54	<0.001
Congruency	0.19	0.04	4.74	<0.001
Group	0.43	0.13	3.29	0.002
Congruency × Group	0.02	0.05	0.41	0.68

Table 6S – Interaction between mean RT (in the congruent control trials) and task on reaction time during congruent trials in the schizophrenia group. The model was defined as: $RT = \beta 0_i + \beta 1_i Task + \beta 2_i MeanRT + \beta 3 TaskMeanRT + \varepsilon$.

Factor	ß	SE	t	p
Intercept	0.44	0.03	13.92	<0.001
Task	-0.25	0.05	-4.60	<0.001
Mean RT	1.09	0.05	23.91	<0.001
Task × Mean RT	-0.25	0.08	-3.22	0.002

Table 7S – Interaction between mean RT (in the congruent control trials) and task on reaction time during congruent trials in the control group. The model was defined as: $RT = \beta 0_i + \beta 1_i Task + \beta 2_i MeanRT + \beta 3 TaskMeanRT + \varepsilon$.

Factor	ß	SE	t	p
Intercept	0.02	0.02	0.85	0.393
Task	-0.06	0.04	-1.48	0.143
Mean RT	1.08	0.06	17.11	<0.001
Task × Mean RT	0.07	0.10	0.65	0.518

Table 8S – Interaction between antipsychotic dose and task on reaction time during congruent trials, when adjusting for other medications and excluding patients who had antipsychotic medication changes within 3 weeks prior to the day of testing. The model was defined as: $RT = \beta 0_i + \beta 1_i Task + \beta 2 CPZ + \beta 3 Antidepressant + \beta 4 Anticholinergic + \beta 5 Corticosteriod + \beta 6 Proton\text{-}pump\text{-}inhibitor + \beta 7 Contraception + \beta 8 Anticonvulsant + \beta 9 NSAID + \beta 10 Benzodiazepine + \beta 11 Simvastatin + \beta 12 TaskCPZ + \beta 13 TaskAntidepressant + \beta 14 TaskAnticholinergic + \beta 15 TaskCorticosteriod + \beta 16 TaskProton\text{-}pump\text{-}inhibitor + \beta 17 TaskContraception + \beta 18 TaskAnticonvulsant + \beta 19 TaskNSAID + \beta 20 TaskBenzodiazepine + \beta 21 TaskSimvastatin + \varepsilon$. Only medications taken by at least three patients were included in the model.

Factor	ß	SE	t	p
Intercept	0.41	0.21	1.93	0.064
Task	-0.20	0.09	-2.30	0.024
CPZ	0.15	0.16	0.92	0.368
Antidepressant	-0.12	0.28	-0.43	0.673
Anticholinergic	-0.60	0.36	-1.69	0.101
Corticosteroid	-0.22	0.39	-0.57	0.573
Proton pump inhib.	-0.61	0.44	-1.41	0.171
Contraception	-0.22	0.39	-0.57	0.573
Anticonvulsant	0.61	0.46	1.33	0.194
NSAID	0.12	0.49	0.24	0.811
Benzodiazepine	0.78	0.49	1.61	0.118
Simvastatin	-0.56	0.46	-1.21	0.236
Task × CPZ	-0.18	0.07	-2.62	0.010
Task × antidepressant	-0.03	0.12	-0.21	0.833
Task × anticholinergic	0.21	0.15	1.45	0.151
Task × corticosteroid	0.14	0.16	0.87	0.388
Task × proton-pump-inh	0.12	0.18	0.65	0.516
Task × contraception	-0.41	0.16	-2.50	0.014
Task × anticonvulsant	-0.01	0.19	-0.07	0.941
Task × NSAID	-0.18	0.21	-0.88	0.382
Task × benzodiazepine	-0.26	0.20	-1.32	0.190
Task × simvastatin	0.01	0.19	0.05	0.959

Table 9S – Interaction between task and antipsychotic dose and symptom severity (SANS, SAPS) on reaction time during congruent trials, excluding patients who had antipsychotic medication changes within 3 weeks prior to the day of testing. The model was defined: $RT = \beta 0_i + \beta 1_i Task + \beta 2SANS + \beta 3SAPS + \beta 4CPZ + \beta 5TaskSANS + \beta 6TaskSAPS + \beta 7TaskCPZ + \varepsilon$.

Factor	ß	SE	t	p
Intercept	0.21	0.15	1.46	0.156
Task	-0.21	0.05	-3.80	<0.001
SANS	0.07	0.20	0.36	0.721
SAPS	-0.02	0.15	-0.15	0.881
CPZ	0.14	0.18	0.78	0.444
Task × SANS	0.07	0.08	0.97	0.340
Task × SAPS	-0.01	0.06	-0.25	0.801
Task × CPZ	-0.17	0.07	-2.47	0.020

Table 10S – Interaction between task and antipsychotic dose and level of functioning (PSP) on reaction time during congruent trials, excluding patients who had antipsychotic medication changes within 3 weeks prior to the day of testing. The model was defined: $RT = \beta 0_i + \beta 1_i Task + \beta 2PSP + \beta 3CPZ + \beta 4TaskPSP + \beta 5TaskCPZ + \varepsilon$.

Factor	ß	SE	t	p
Intercept	0.25	0.20	1.22	0.234
Task	-0.33	0.07	-4.46	<0.001
PSP	0.06	0.18	0.31	0.757
CPZ	0.19	0.17	1.10	0.282
Task × PSP	-0.14	0.06	-2.18	0.032
Task × CPZ	-0.19	0.06	-3.05	0.003

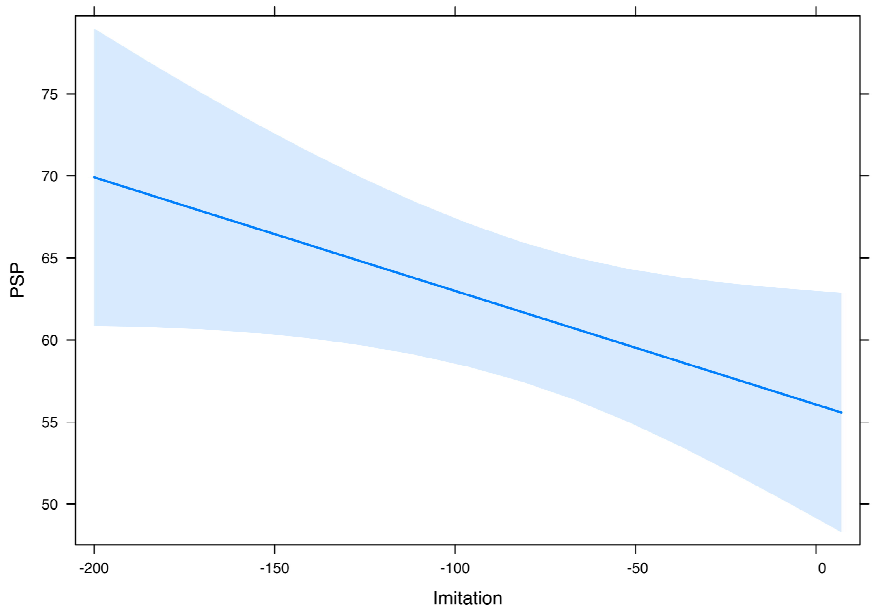

Figure 1S. Marginal relation between imitation (compared to the control condition) on the x-axis and level of functioning (PSP) on the y-axis after controlling for antipsychotic medication dose. Note, the negative values on the x-axis indicate faster reaction times to the imitation task compared to the control task. Marginal effects were estimated following Fox (2003)[18].

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